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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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CATHRYN CAMPBELL
CAMPBELL & FLORES LLP
SUITE 700
4370 LA JOLLA VILLAGE DRIVE
SAN DIEGO CA 92122

EXAMINER	
NICHOLS, J	
ART UNIT	**PAPER NUMBER**
1642	4
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/350,518	Applicant(s) Reed et al.
	Examiner Jennifer Nichols, Nee Hunt	Group Art Unit 1642

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-49* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-49* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Specification

The specification is objected to because it makes contradictory statements. Page 5 and 6 recite concurrently, where determination of high BAG expression correlates to both increased and decreased risk of cancer spread or reoccurrence. This is confusing. Further clarification is required.

Further, on pages 32-36 of the specification, BAG-1 levels were tested, but it is never clear what isoform of BAG-1 is tested, or which antibody is used and what that antibody binds. Variations in protocol may have a significant effect on the outcome of the test an thus further clarification is required. For the purposes of examination, it is assumed that the isoform BAG1 and corresponding monoclonal antibody taught in *Takayama et al., Cancer Research, Vol 38, page 3116* were used.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 9-10, 18 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9 and 10 are unclear in the recitation of BAG-1 and BAG-1N respectively. It is not clear from the specification what isoforms of BAG these refer to. The specification sites *Takayama et al., Cancer Research, Vol 38, page 3116*, however *Takayama et al.* does not teach BAG-1N.

Claim 18 recites the limitation "said BAG protein". There is insufficient antecedent basis for this limitation in the claim.

Claim 47 is unclear in that it fails to correlate how the comparison of BAG expression levels indicates effectiveness of treatment.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 16-37, and 44-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting increased BAG-1 (*the truncated form taught in Takayama et al., Cancer Research, Vol 38, page 3116, abstract*) as an indicator of increased overall survival or distant metastasis free survival in Stage I or Stage II breast cancer patients, does not reasonably provide enablement for detection of an increase or decrease in any and all

BAG gene expressions as an indicator of prognosis, risk of recurrence, risk of metastasis, or monitoring treatment effectiveness for any and all cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

The specification discloses that increased levels of BAG-1 gene expression detecting using a monoclonal antibody to the isoform BAG-1 (a truncated form of the full protein) predicts increased overall survival or distant metastasis free survival in patients with Stage I or Stage II breast carcinoma.

The claims recite methods of detection of an increase in any and all BAG gene expressions as an indicator of decreased risk of metastasis or recurrence for any and all cancer. The claims also recite methods of detection of a decrease in BAG gene expressions as an indicator of increased risk of metastasis or recurrence for any and all cancer.

The prior art teaches that in many cancers, increased BAG expression is correlated with poor prognosis and increased risk of distant metastasis and tumor recurrence. *Tang et al., Journal of Clinical Oncology, Vol 17, No 6, pages 1710-1719, (June 1999)* teaches that increased

BAG-1 expression was significantly associated with shorter disease free and overall survival in all stages of breast cancer (table 4, page 1718). The results of *Tang et al.* are in direct contradiction with those of the instant application, which illustrates how even minute differences in experimental technique can alter the conclusions drawn from the study. Further, *Zapata et al., Breast Cancer Research and Treatment, Vol 47, pages 129-140 (1998)* teaches that BAG-1 levels are higher in invasive breast cancers (page 138, 1st column, 3rd paragraph). *Yawata et al., Oncogene, Vol 16, pages 2681-2686 (1998)* teaches that increased BAG-1 levels promote metastasis in colon cancer (abstract and page 2681, 2nd column, last paragraph). Additionally, *Takaoka et al., Oncogene, Vol 14, pages 2971-2977* (1997) teaches that overexpression of BAG-1 promotes pulmonary metastasis of melanoma (abstract).

Therefor the art teaches that increased levels of BAG expression do not indicate decreased risk of metastasis or recurrence for any and all cancers and likewise that decreased levels of BAG expression do not indicate increased risk of metastasis or recurrence for any and all cancers. Similarly, detection of the different isoforms of BAG have lead to differing conclusions about breast cancer prognosis. Thus because the art sets forth specific examples in which the full scope of the instant claims are not enabled, one of ordinary skill in the art at the time the invention was made would not have been enabled to practice the full scope of the claimed invention.

5. Claim 23 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 23 recites comparison to in vitro levels for the relative determination of BAG expression. The specification fails to provide any guidance or objective evidence that in vitro measurements allow relative determination of BAG expression in cells. Further, the specification specifically sets forth that in vitro reference levels are unreliable (see page 18, 2nd paragraph). Therefor one of ordinary skill in the art would not be able to practice the invention as recited in the instant claim.

6. Claim 47 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 47 recites a method of determining effectiveness of treatment by measuring BAG gene expression levels before and after the treatment. The specification fails to provide any guidance or objective evidence that such a comparison would enable a determination of treatment effectiveness. BAG expression levels are only measured once and thus no correlation can be made. There is no objective evidence or guidance which would indicate that increasing or decreasing BAG expression levels indicated effectiveness of treatment and thus one of ordinary skill in the art would not have been enabled to practice the claimed invention.

7. Claims 48 and 49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 48 and 49 recite determining prognosis of disease free or overall survival by determining BAG activity. The specification fails to provide any guidance or objective evidence that BAG activity would enable a determination of prognosis of disease free or overall survival. The level of BAG activity is never measured or compared to cancer prognosis, nor is any evidence presented which would lead to the determination that BAG activity would be useful for determining the recited prognosis. Further, even if BAG activity level did correlate to prognosis, determination of a level of a specific compound which acts with or on BAG, such as HIP would not necessarily provide accurate information about BAG activity, since BAG acts in concert with a multitude of compounds (*Takayama et al., The Journal of Biological Chemistry, Vol 274, No 2, page 786, last paragraph*). Therefor one of ordinary skill in the art would not be enabled to practice the invention as claimed.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-2, 5-11, 13, 15-17, 19-21, 24-28, 31-32, 34-36 and 42-46 are rejected under 35 U.S.C. 102(a) as being anticipated by *Krajewski et al., Endocrine Related Cancer, Vol 6, No 1, pages 29-40, March 1999.*

Krajewski et al. teaches a method of determining overall survival and risk of recurrence of early stage breast cancer by determining levels of the BAG protein and correlating increased BAG-1 protein expression with increased overall survival or decreased risk of recurrence. The method uses an immunoassay, specifically a monoclonal antibody which binds all known isoforms of the BAG protein to determine expression. Levels of expression in malignant cells is compared the reference of non-tumor cells.(page 36, first column, second and third paragraph) Lastly, Krajewski et al. teaches that the method is useful for determining and optimizing treatment (page 37, last paragraph)

9. Claims 1, 3-4, 6-11, 13-15, 42-43, and 45-46 are rejected under 35 U.S.C. 102(a) as being anticipated by *Tang et al., Journal of Clinical Oncology, Vol 17, No 6, June 1999.*

Tang et al. teaches a method of determining overall survival and risk of recurrence of all stages of breast cancer by determining levels of the BAG protein and correlating increased BAG-1 protein expression with decreased overall survival or increased risk of recurrence. (Page 1716, first paragraph) The method uses an immunoassay, specifically an antibody which binds the BAG protein to determine expression.(page 1711, last paragraph)

10. Claims 1, 3-4, 6-11, 13-15, 42-43, and 45-46 are rejected under 35 U.S.C. 102(b) as being anticipated by *Zapata et al., Breast Cancer Research and Treatment, Vol 47, 129:140, January 1998.*

Zapata et al. teaches a method of determining overall survival and risk of recurrence of all stages of breast cancer by determining levels of the BAG protein and correlating increased BAG-1 protein expression with decreased overall survival or increased risk of recurrence. (Page 138, 3rd paragraph) The method uses an immunoassay, specifically a monoclonal antibody which binds the BAG protein to determine expression.(page 131, 2nd paragraph)

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-2, 5-13, 15-21, 24-36, and 38-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Krajewski et al., Endocrine Related Cancer, Vol 6, No 1, pages 29-40, March 1999,* in view of *Sano et al., US Patent 5,665,539 (March 16, 1999), An et al., 5,882,864 (March 16, 1999), or Ravdin et al., US Patent 5,862,304 (January 19, 1999).*

Krajewski et al. teaches as applied to claims 1-11, 13, 15-17, 19-21, 24-28, 31-32, 34-36, and 42-46 supra. Krajewski et al. fails to teach the art known assays, statistical analysis and kits of the instant claims. Specifically, Krajewski et al. fails to teach techniques of detection of BAG using immuno-PCR or detection of mRNA using probes. Krajewski et al. also fails to teach determination of the reference value using histogram analysis and the corresponding reagents and kits to the aforementioned detection systems.

Detection of a protein using immuno-PCR, or of mRNA using a probe are techniques well known in the art, as taught by Sano et al.(see abstract), or An et al.(column 34, line 32-column 36, line 38). Use of histogram analysis to develop a standard using a large amount of data is also well known, as taught by Ravdin et al. (see abstract).

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art to combine the methods of Krajewski et al. and the detection techniques of Sano et al., An et al., or Ravdin et al. and one would have been motivated to do so because these are useful and efficient methods of detection of a protein or gene. Further, it is prima facie obvious to package the reagents useful for a method in a convenient kit form for the purpose of increased marketability convenience, reliability, and economy.

13. Claims 1, 3-4, 6-15, 38-43, and 45-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Tang et al., Journal of Clinical Oncology, Vol 17, No 6, June 1999,* in view of *Sano et al., US Patent 5,665,539 (March 16, 1999).*

Tang et al. teaches as applied to claims 1, 3-4, 6-11, 13-15, 42-43, and 45-46 supra. Tang et al. fails to teach detection of BAG using immuno-PCR and the corresponding reagents and kits to the aforementioned detection systems.

Detection of a protein using immuno-PCR is a techniques well known in the art, as taught by Sano et al.(see abstract).

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art to combine the methods of Tang et al. and the detection techniques of Sano et al. and one would have been motivated to do so because these are useful and efficient methods of detection of a protein. Further, it is prima facie obvious to package the reagents useful for a method in a convenient kit form for the purpose of increased marketability convenience, reliability, and economy.

14. Claims 1, 3-4, 6-15, 38-43, and 45-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Zapata et al., Breast Cancer Research and Treatment, Vol 47, 129:140, 1998,* in view of *Sano et al., US Patent 5,665,539 (March 16, 1999).*

Zapata et al. teaches as applied to claims 1, 3-4, 6-11, 13-15, 42-43, and 45-46 supra. Zapata et al. fails to teach detection of BAG using immuno-PCR and the corresponding reagents and kits to the aforementioned detection systems.

Detection of a protein using immuno-PCR is a techniques well known in the art, as taught by Sano et al.(see abstract).

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art to combine the methods of Zapata et al. and the detection techniques of Sano et al. and one would have been motivated to do so because these are useful and efficient methods of detection of a protein. Further, it is prima facie obvious to package the reagents useful for a method in a convenient kit form for the purpose of increased marketability convenience, reliability, and economy.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Nichols, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell can be reached at (703) 308-4310. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**paulahutzell@uspto.gov**].

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that sensitive information could be identified or exchanged unless the record includes a properly

signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Nichols, Nee Hunt

January 17, 2000

PAULA K. HUTZELL
SUPERVISORY PATENT EXAMINER